AD________________

Award Number: W81XWH-12-1-0143

TITLE: Social Resources that Preserve Functional Independence after Memory Loss

PRINCIPAL INVESTIGATOR: Dr. M. Maria Glymour

CONTRACTING ORGANIZATION:
University of California San Francisco

San Francisco, CA 94143

REPORT DATE: May 2014

TYPE OF REPORT: Annual report

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE May 2014	**2. REPORT TYPE** Annual	**3. DATES COVERED** 20 April 2013 – 19 April 2014
4. TITLE AND SUBTITLE: Social Resources that Preserve Functional Independence after Memory Loss		**5a. CONTRACT NUMBER**
		5b. GRANT NUMBER W81XWH-12-1-0143
		5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S) Dr. M. Maria Glymour		**5d. PROJECT NUMBER**
		5e. TASK NUMBER
E-Mail: mglymour@psg.ucsf.edu		**5f. WORK UNIT NUMBER**
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) University of California San Francisco, Dept of Epidemiology and Biostatistics, San Francisco, CA 94143		**8. PERFORMING ORGANIZATION REPORT NUMBER**
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command, Fort Detrick, Maryland 21702-5012		**10. SPONSOR/MONITOR'S ACRONYM(S)**
		11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT *(Enter a brief (approximately 200 words) unclassified summary of the most significant finding during the research period.)*

We used a large, diverse, longitudinal study of middle aged and older Americans to identify social factors that help individuals preserve functional independence in basic and instrumental ADLs as long as possible, even in the context of declining memory or severe memory impairment. As expected, we found strong associations between decreased cognitive functioning and incident ADL and IADL limitations. We also found that physical activity may help to decrease the risk of ADL and IADL limitations even among those with cognitive impairment, while smoking and depression may increase the risk of incident ADL limitations among those with cognitive impairments. This finding has critical importance for clinicians, patients, and family members of individuals with cognitive impairments or incipient dementia. By managing conventional risk factors, it may be possible to stave off dependencies, maximize quality of life, and minimize caregiver burden. This is especially important for older veterans and those with prior exposure to mild, moderate, or severe TBI, who are at elevated risk of memory loss and dementia.

<table>
<tr><td colspan="6">15. SUBJECT TERMS (Key words or phrases identifying major concepts in the report) Subject terms are keywords that may have been previously assigned to the proposal abstract or are keywords that may be significant to the research.
Cognitive impairment, Functional Limitations, Individual-level resilience factors</td></tr>
<tr><td colspan="3">16. SECURITY CLASSIFICATION OF:</td><td rowspan="2">17. LIMITATION OF ABSTRACT
UU</td><td rowspan="2">18. NUMBER OF PAGES
33</td><td>19a. NAME OF RESPONSIBLE PERSON
USAMRMC</td></tr>
<tr><td>a. REPORT
U</td><td>b. ABSTRACT
U</td><td>c. THIS PAGE
U</td><td>19b. TELEPHONE NUMBER (include area code)</td></tr>
</table>

Table of Contents

1. INTRODUCTION

Memory losses are common among long-term survivors of traumatic brain injury (TBI) and TBI has been linked to increased risk of memory impairment and dementia. This is an important determinant of long-term well-being for military service men and women and their families, because of the elevated incidence of TBI in combat areas. Memory and cognitive impairments predict substantial losses in ability to independently manage daily activities; this loss of independence can be devastating to the individual and his or her family. To avoid dependence, we need to identify factors which preserve independence even in the face of memory and cognitive losses. While studies have examined predictors of institutionalization among those with dementia(*1*), factors like depression which predict institutionalization may be undertreated among those with dementia.(*2*) It is not known whether managing these risk factors among individuals with cognitive impairment is important because little research has been done on whether resources at personal and environmental levels can modify the translation of impairments caused by neurodegenerative diseases into functional disabilities. Current understanding of disability emphasizes that physical impairments in body functioning or structure do not necessarily induce functional disability because environmental, behavioral, and instrumental accommodations can foster continued independence.(*3*) Figure 1, an adaptation of the disablement process model by Verbrugge and Jette(*4*), demonstrates the process by which illness pathology and cognitive impairment may lead to functional limitations and disability. However, individual level modifiers for example, physical activity or not being depressed, and family level modifiers for example, spouse's education and contacts with friends and family, may also influence functional limitations and the individual's ability to use accommodations or coping strategies and may help promote functional independence even among individuals with memory loss or dementia. This project uses data from the nationally representative Health and Retirement Study (HRS), a large, diverse, longitudinal study of middle aged and older Americans, to identify modifiable individual- and family-level factors that help individuals preserve functional independence as long as possible even in the context of declining memory or cognitive impairment.

2. KEYWORDS

Disability, memory loss, caregiving, inverse probability weighting, instrumental activities of daily living, basic activities of daily living, dementia, social support, physical activity, depression, alcohol use.

3. KEY RESEARCH ACCOMPLISHMENTS

- Developed inverse probability weighting models to statistically account for selective survival and dropout.
- Completed statistical programming, specified core statistical models and derived preliminary estimates of the association between cognitive loss as measured by a dementia probability score and changes in functional independence as measured by five Activities of Daily Living (ADL) and five Instrumental Activities of Daily Living (IADL) in Health and Retirement Survey (HRS) cohort members.
- Tested individual level resiliency factors as modifiers of the effects of cognitive impairment on ADL limitations using pooled logistic regression and Poission regression as well as inverse probability weighting.
- Published a manuscript on cognitive impairment, individual-level modifiers and incident ADL limitations.
- Draft a manuscript on cognitive impairment, individual-level modifiers and incident IADL limitations.

- Submit abstracts to the American Academy of Neurology Annual Meeting and the Society of Epidemiological Research Annual Meeting
- Linked family level variables and tested family level resiliency factors as modifiers of the effects of memory functional impairments

3a. What were the major goals of the project?

3a. Tasks and status

We proposed three specific aims to be addressed in this cohort:

1. Identify *individual-level resilience factors* that ameliorate the impact of memory loss on functional independence, considering health behaviors (physical activity, alcohol use, and smoking), socioeconomic resources (income), and mental health (depressive symptoms).
2. Identify *family-level resilience factors* that ameliorate the impact of memory loss on functional independence, considering living arrangements (living alone, with a spouse, with other family, or with non-family), spousal characteristics (spouse's mental health, spouse's employment status), and social contacts (proximity and contacts with family and close friends).
3. Identify *community-level resilience factors* that ameliorate the impact of memory loss on functional independence, considering region of the country, neighborhood ties (years residing in the community, contacts with neighbors), and neighborhood conditions (density, walkability, age distribution of neighborhood residents).

3a. What was accomplished under these goals?

In summary, to date, we have completed task 1. One manuscript on these findings was recently published in *Neurology* and another manuscript is under review. Task 2 is in process. Progress was delayed while we awaited the transfer of the grant from Harvard to UCSF, but we continued work that was already in progress (i.e., work that would have caused substantial loss of progress if interrupted). We are in the "clean up" stage of analyses for task 2, as we conduct sensitivity analyses and prepare the manuscript. Work on Task 3 is just beginning.

To provide more detail, in order to accomplish the tasks outlined above, we first completed an analysis examining the impact of individual level modifiers on the association between cognitive impairment and incident ADL limitations. The complete manuscript reporting results of this analysis ("Dementia and dependence: Do modifiable risk factors delay disability?") was recently published in *Neurology* and is available as an appendix. In brief, we used data from individuals enrolled in the Health and Retirement Study. The analytic sample included 4,922 Health and Retirement Study participants aged 65+ without limitations in activities of daily living (ADLs) at baseline. Participants were interviewed biennially up to 12 years. Cognitive status was assessed through a dementia probability score and a memory score, both of which were estimated from composites of direct and proxy assessments. Methods for calculating these scores have been described in detail elsewhere.(*5*) We divided the dementia probability score and memory score into four categories representing low, mild, moderate or high probability of developing dementia or of having memory impairments. Our outcome was reported difficulty in any of the five activities of daily living (getting across a room, dressing, bathing, eating, and getting in and out of bed) in the past 30 days. Hypothesized modifiers were self-reported physical activity, smoking, alcohol consumption, depression and income.

We used pooled logistic regression models with inverse probability weights to adjust for time-varying confounding to assess multiplicative and additive interactions of dementia category with each modifier in predicting incident ADL limitations. As expected, higher dementia score category was associated with an increased risk of ADL limitations (OR=1.65, 95% CI: 1.49-1.83

per category increase). On a relative scale, physical inactivity was associated with an increased risk of incident ADL limitations among those with low dementia probability (OR-1.51, 95% CI: 1.25, 1.81). However, the interaction between physical activity and dementia probability was close to 1 and not significant, indicating that the estimated relative harm of low physical activity was similar regardless of dementia category.

In our next set of analyses, we calculated the marginal probability of develop any icdent ADL limitations for each combination of modifier status and low or high dementia risk. These analyses address the impact of the modifiers on an absolute scale. We observed that smoking, not drinking and low income have larger adverse effects on the absolute probability of developing incident ADL limitations among those with high dementia probability than among those with low dementia probability. This suggests that even among individuals with substantial cognitive impairment managing conventional risk factors is very important and may provide a way to stave off dependencies, maximize quality of life and minimize caregiver burden.

In addition to containing data on ADL limitations, the HRS cohort also assessed limitations in Instrumental Activities of Daily Living (IADLs). IADLs are often considered to be more cognitively demanding than ADLs. (*6*) Because of this, we thought the impact of our individual level modifiers may be different for ADLs versus IADLs. Additionally since there are many ways of analyzing functional outcomes data, we explored using a different analysis technique to analyze our IADL data. We have performed a second set of analyses using limitations in IADLs as our outcome and have draft a separate manuscript to present these results. Our methods and results are outlined below.

Similar to the ADL analysis, we examined the impact of both memory score and dementia probability status on our outcome. We categorized memory and dementia status based on quartiles of their distributions at baseline. These categories were modeled as indicator variables due to the non-linear associations between memory impairment and incident IADL limitations. Since we were interested in examined the effect of our modifiers among those who are cognitively impaired, worst memory function or high dementia probability were used as the reference group for all analyses. Results for memory and dementia were similar so we will only discuss the results for memory status below.

We used the same modifiers as those used in our ADL analyses (physical activity, smoking, alcohol consumption, depression and income). Our exposure and modifier status was also assessed in the wave prior to our outcome assessment.

For our outcome, we used limitations in the past 30 days in IADLs. The IADLs assessed in HRS were using a telephone, taking medication, handling money, shopping and preparing meals. Possible response options were yes, no, or do not do, which was treated as missing in this analysis.

While pooled logistic regression with inverse probability weighting is the most appropriate technique for analyzing binary outcome events, it cannot handle count data. This is potentially a limitation since it is possible that an individual may have multiple IADL limitations. In this scenario the outcome would be a "count" instead of a binary outcome. To analyze count data, we must use Poisson regression. To correct for overdispersion and clustering, we used sandwich variance estimators. (*7*) Each year, we counted the total number of IADL limitations reported by an individual and used this count as our outcome variable. First we tested the association between cognitive status and incident IADL limitations. Next, we assessed multiplicative interactions of each modifier with dementia in predicting IADL limitations.

From the 10,367 individuals aged 65 or older in 1998, we excluded the 3391 participants who did not answer any of the questions on IADL limitations in 1998 or who reported any IADL limitations in 1998 or 2000. We also excluded 747 participants who did not answer the question on IADL limitations in 2002 and 453 participants for whom memory or other cognitive measures were not available in 1998 or 2000. Finally, we excluded 355 participants missing baseline covariate information, leaving 5219 participants for our analyses.

Respondents with the worst memory functioning at baseline had a higher prevalence of physical inactivity, smoking, not drinking, and depression at baseline compared to those with better memory functioning (Table 1). Individuals with the worst memory functioning reported the highest mean number of limitations at each wave (Table 2).

The best memory functioning category was associated with decreased risk of incident IADL limitations (relative risk=0.41, 95% CI: 0.27-0.65). Compared to low memory functioning, moderate memory functioning (relative risk=0.35; 95% CI: 0.26-0.46) and poor memory functioning (relative risk=0.49; 95% CI: 0.40-0.60) were also associated with significant decreases in the risk of incident IADL limitations.

Table 3 shows the association between our memory categories and the risk of incident IADL limitations, the association between each modifier and incident IADL limitations, and the interaction between each memory category and each modifier. In these models, an interaction coefficient of 1 indicates the modifier has the same relative effect on IADL limitations in those with low memory as in those with higher memory functioning. If the interaction coefficient is less than 1, it indicates the modifier effect is lower (less harmful) among those with higher memory functioning; conversely, if the interaction coefficient is greater than 1, it indicates the modifier effect is higher (more harmful) among those with higher memory functioning.

Physical inactivity predicted higher increased risk of incident IADL limitations among those with memory impairment (RR=1.47; 95% CI: 1.12, 1.95). The interaction between physical inactivity and high memory was over 1 (RR=1.91, 95% CI: 0.98, 3.74) indicating that the estimated relative harm of physical inactivity may be greater among those with high memory functioning than among those with the worst memory functioning, although this interaction was not statistically significant. Other modifiers were not significantly associated with increased risk of IADL limitations among those with the worst memory. The interaction terms between these modifiers and our memory categories were not statistically significant, so there was also no evidence that the relative harm of these modifiers differed by memory functioning.

Next we explored whether the modifiers have different absolute effects on the risk of incident IADL limitations for individuals in different memory categories. Respondents in the worst memory category who were physically active were predicted to develop an average of 0.28 incident IADL limitations over the next two years (Figure 1). However, expected outcomes were much worse for those in the worst memory category who were physically inactive. They were predicted to develop an average of 0.42 new IADL limitations within the next two years. Physical activity was thus estimated to reduce the average number of incident IADL limitations by 0.14 (p-value for difference < 0.01) among individuals in the worst memory category. Among people in the best memory category, those who were physically active were predicted to develop an average of 0.07 incident IADL limitations within the next two years, while those who were not physically active were predicted to develop an average of 0.19 incident IADL limitations within the next two years. Physical activity reduced the average number of incident IADL limitations by 0.12 for those in the best memory category (p-value for difference < 0.01). The estimated absolute benefit of physical activity was similar among those in the worst memory category as among those in the best memory category and beneficial for both. For individuals in the middle two quartiles of memory functioning, physical activity was not significantly associated with IADL limitations for either group (p-values>0.51)

Individuals in the worst memory category who did not drink had higher risk of incident IADL limitations than individuals with similar memory who did drink (p-value=0.045), but the apparent benefits of moderate alcohol use were not observed in the other memory categories. Current smoking and depression had larger absolute adverse effects among those with the best memory than among those with the worst memory but these effects were not statistically significant. Current smoking and depression had little effect on the absolute risk of IADL limitations for those in the middle two quartiles of memory functioning.

In conclusion, we found a strong association between memory and incident IADL limitations. Physical inactivity was associated with an increased risk of incident IADL limitations even among the cognitively impaired. Maintaining physical activity should be a high priority for individuals with cognitive impairment as well as their families and clinicians because it may help to stave off dependency.

Our previous analyses have focused on the role of individual-level factors on ameliorating the impact of cognitive impairment on functional limitations. However, extensive evidence suggests that social networks also influence various domains of health, with some evidence of special importance of spouses and friends for older adults. However, little is known about whether these associations prevail for onset of instrument and basic activities of daily living (I/ADLs) and whether they differ for individuals with memory impairment. The objective of the next part of our project was to determine whether family-level factors reduce the risk of incident I/ADLs and whether these association differ for individual with high versus low memory function. We present an overview of our methods and results below.

We had two primary outcomes which were analyzed in separate models. First we examined any ADL limitation as our outcome and then we analyzed any IADL limitation as our outcome. During the biennial interviews, participants or proxy respondents reported whether they had difficulty in the past 30 days in five ADLs (getting across a room, dressing, bathing, eating, and getting in and out of bed) and in five IADLs (using a phone, managing money, taking medication, shopping for groceries, and preparing hot meals). Participants reported “yes”, “no”, or “do not do” for each of these items. We used the RAND variables for any ADL limitation and any IADL limitation(*8*). “Do not do” and “refused” are treated as missing in the RAND coding. Participants who reported any ADL or IADL limitations in 1998 or 2000 were excluded from our analyses.

The family-level variables we examined in this study were living arrangements, proximity to children, contacts with friends, spouse’s depression status, spouse’s employment status, and spouse’s education status. Since the use of inverse probability weights (see below) requires one wave of run-in, all exposure variables were assessed in 2000. In the event that information on the variable was missing in 2000, we used information from 1998.

Living arrangements were classified as living with spouse (reference category), living with child or others, and living alone. Proximity to children was classified as living with children (reference category), having no children, living within 10 miles of children, living over 10 miles from children. Contact with friends was defined as at least weekly meetings with friends (reference category) versus less than weekly meetings with friends. Spouse’s depression status was categorized as non-depressed spouse (reference category), depressed spouse, and no spouse. Depressed spouse was defined as reporting ≥3 depressive symptoms on a modified 8-item Centers for Epidemiologic Studies-Depression (CES-D) scale in the past two weeks. Spouse’s employment status was categorized as retired (reference category), working full-time, working part-time, not working or disabled, and no spouse. Spouse’s educational status was classified as having no degree, having a high school diploma or GED (reference category), having a bachelor’s degree or higher, or no spouse.

In addition to assessing family-level covariates in 2000, we also assessed memory status in 2000. Our measure of memory status was imputed memory score which was calculated using methods described in detail elsewhere(*5*). Briefly, the imputed memory score is calculated by combining directly and proxy-assessed memory status into a composite memory assessment which was calibrated against a multi-instrument memory assessment. The imputed memory score ranges from -2 (worst memory) to 2 (best memory). We divided the memory score into two categories based on the 25th percentile of the memory score distribution in 1998 and included this categorical variable in all models.

In addition to adjusting for memory status, we also adjusted for a number of individual characteristics, demographics, health behaviors, and comorbidities. All of these potential confounders were assessed in 1998 (the wave prior to family-level variable assessment) and included: age (centered, continuous), centered age squared (continuous), gender, race (black versus other), southern birthplace, years of education (linear spline model with discontinuities at completion of high school and completion of college plus an indicator variable for GED completion), mother's and father's education (=<8 years, >8 years), and height (gender-specific baseline quartiles), log of household size-adjusted wealth (continuous), log of household size-adjusted income (continuous), body mass index (continuous), self-reported comorbidities (high blood pressure, diabetes, cancer, lung disease, heart disease, stroke, psychiatric problems, and arthritis), physical activity (active versus inactive), alcohol consumption (moderate versus non-moderate drinking), current smoking (yes/no), depression (yes/no where yes was defined as reporting ≥3 depressive symptoms on a modified 8-item Centers for Epidemiologic Studies-Depression (CES-D) scale in the past two week), and interview wave. Participants missing any covariate in 1998 were excluded from all analyses. If a covariate value was missing during follow-up, we carried forward the last known value of the covariate.

We ran separate pooled logistic regression models for any ADL limitation and for any IADL limitation. Pooled logistic regression approximates the Cox proportional hazards model when dealing with discrete time data and rare outcomes. For our ADL analyses, participants were censored from analyses after developing an ADL limitation, last interview, death or the first wave of missing information on memory of ADL limitation. Similarly, for our IADL analyses, participants were censored from analyses after developing an IADL limitation, last interview, death or the first wave of missing information on memory of IADL limitation. All analyses were performed using PROC SURVEYLOGISTIC in SAS 9.2 (SAS Institute, Cary, NC) with weights as described below.

To account for selection and attrition during the course of the study, we used inverse probability weights. The inverse probability weights require one wave of "run-in" so our first exposure wave was in 2000 and the first outcome was in 2002. Weights for survival and participation as well as the HRS sampling weight from 1998 were multiplied together to create a final weight for each participant. This final weight reflects the inverse of the probability that the individual was alive and participated in the outcome wave and had the family-level variable value he or she actually had, given his or her past family-level variable and covariate history. Weights were stabilized(*9*) and truncated at the 98th percentile to minimize outlier influence.

In addition to examining whether our family-level modifiers were associated with incident I/ADL limitations, we also explored whether our family-level factors had different effects on the risk of I/ADL limitations among those with better memory functioning compared to those with worst memory functioning. This was done by including an interaction term between memory status and each family-level variable in separate models for each family-level variable. This tests whether the modifier has different relative effects on IADL or ADL limitations depending on the participant's memory status.

Of the 10,367 participants aged 65 years or older in 1998, we excluded 4572 people who either had an ADL or IADL limitation in 1998 or 2000 or who did not answer the questions on I/ADL limitations in 1998 or 2000. Next we excluded the 578 people who did not answer the questions on I/ADL limitations in 2002. Then we excluded the 379 people missing information on imputed memory score in 1998 or 2000. Finally, we excluded the 738 people missing information on our covariates at baseline which left 4100 people for our final analyses.

Those with poor memory at baseline were less likely to live with their spouse compared to those with normal memory (Table 4). 1500 people reported any ADL limitation and 1496 people reported any IADL limitation during the course of the study.

Table 5 shows the associations between our family-level variables and the risk of incident ADL or IADL limitations. Most of the family-level variables were not significantly associated with the risk of incident ADL or IADL limitations. Having a depressed spouse compared to a non-depressed spouse was significantly associated with an increased risk of incident ADL limitations (RR=1.37, 95% CI: 1.03, 1.82) but not IADL limitations (RR=1.12, 95% CI: 0.81, 1.55). Additionally, having a spouse with less than high school education compared to a spouse with a high school diploma was associated with a decreased risk of incident ADL limitations (RR=0.76, 95% CI: 0.62, 0.94). However, having a spouse with less than high school education increased the risk of IADL limitations (RR=1.24, 95% CI: 1.00, 1.54; p-value=0.052).

We also explored whether the association between our family level values and incident I/ADL limitations may vary by cognitive status. Although, normal memory functioning was associated with a decreased risk of incident ADL and IADL limitations in all models, we did not observe any significant interactions between our family-level variables and memory status (Table 6). We did see some evidence though that less than weekly contact with friends may increase the risk of ADL (RR=1.28; 95% CI: 0.99, 1.67) and IADL limitations (RR=1.24, 95% CI: 0.96, 1.59) for those with cognitively impairment. This suggests that contacts with friends may be particularly beneficial for those who are cognitively impaired.

We have begun to draft a manuscript presenting these results and hope to submit the manuscript to a gerontology journal this summer. Due to delays in hiring a post-doctoral researcher and research assistant at the University of California San Francisco for this project, we have not yet begun work on the final task examining community level risk factors. Since the grant has been transferred to UCSF, we can hire these individuals and begin the research for these analyses.

What opportunities for training and professional development has the project provided?

Nothing to report.

How were the results disseminated to communities of interest?

Our primary method of dissemination is presentation of research findings at professional conferences and scientific journals. As described above, we have presented at the American Academy of Neurology, the Society for Epidemiologic Research, and published our first manuscript in the journal Neurology.

What do you plan to do during the next reporting period to accomplish the goals?

Our top priority in the coming year is to finalize manuscripts on family level resources and onset of disability and to begin work on the neighborhood risk factors and risk of disability. While the grant was suspended, during the transfer from Harvard to UCSF, we engaged in minimal activities to keep the core of the grant functional. These included responding to journal revision requests on manuscripts to ensure that the grant suspension did not compromise the scientific progress already achieved. We also used other funding sources to supplement activities as needed. Given this, we have substantially underspent in the previous year. We would like to carry forward this excess, and will use it to expand the size of the cohort included in the analyses, i.e., increase accrual, based on data that have only recently become available. Thus, an additional goal is to link to the newly available data.

4. IMPACT

Our primary goal is to impact care for adults with memory loss or memory impairment to help these individuals maintain functional independence. This could benefit the care recipient as well as his or her loved ones and caregivers, and reduce the financial impact of providing optimal care to memory impaired individuals. We have no formal evaluation of whether our first research findings are having such an impact, but we are optimistic because they were published in a leading journal, read by clinicians who provide care for memory impaired patients. The article was also chosen for the "In Focus" spotlight in the April 29, 2014 issue of Neurology.

Methodologically, we believe our research methods correctly handle a major source of bias in studies of dementia and closely related outcomes. Specifically, cognitive impairment is such a strong predictor of mortality and study attrition, that in studies in which cognitive impairment is either a predictor or an outcome, selective attrition can result in spurious findings or obscure true effects. We implemented inverse probability weights to address this challenge, and we believe this approach or a set of closely related tools will be influential for improving the observational research in this area.

5. CHANGES/PROBLEMS

The major challenge experienced in the past year has been suspension of the grant pending transfer from Harvard to UCSF. While the grant was suspended, we engaged in minimal activities to keep the core of the grant functional. These included responding to journal revision requests on manuscripts to ensure that the grant suspension did not compromise the scientific progress already achieved. We also used other funding sources to supplement activities as needed. Given this, we have substantially underspent in the previous year. We would like to carry forward this excess, and will use it to expand the size of the cohort included in the analyses, i.e., increase accrual, based on data that have only recently become available.

An additional challenge this year is the need to hire a new programmer. We now anticipate that the logistical challenges of continued work with Dr. Pamela Rist, who has been a superb analyst on this project but resides in Boston, will necessitate finding a new analyst who is located in San Francisco. We will seek a candidate with familiarity with the HRS data set and the statistical methods in order to ensure a smooth transition. A final challenge has been the ongoing difficulty in hiring a suitable research assistant. We plan to post a position for this for the coming year in effort to find an appropriate person. This may be easier in the San Francisco area than it proved at Harvard.

6. REPORTABLE PRODUCTS

- Published a manuscript on our results for cognitive impairment, individual-level modifiers and incident ADL limitations in *Neurology*

- Revised a manuscript on our results for cognitive impairment, individual-level modifiers and incident IADL limitations based on reviewer critiques; we will submit manuscript again by June 2014

- Abstract entitled: "Forgetful but Not Disabled: Predictors of Incident IADL Limitations" was presented as a poster at the American Academy of Neurology Annual Meeting in Philadelphia April 26-May 3, 2014

- Abstract entitled: "From forgetful to disabled: Does physical inactivity accelerate onset of IADL limitations among memory impaired adults?" was accepted for presentation as a poster an the upcoming Society for Epidemiologic Research Annual Meeting in Seattle June 24-27, 2014

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

Individuals who have been involved in the project include:

Dr. Maria Glymour (PI)

Dr. Pamela Rist (Programmer/Analyst, Post-doctoral researcher)

Jessica Marden (nee Daniel; research assistant)

No other organizations have been involved since the grant transfer to UCSF.

8. CONCLUSION

We found strong associations between decreased cognitive functioning and incident ADL limitations. Smoking, not drinking, and having low income may increase the risk of incident ADL limitations among those with cognitive impairments. We also observed a strong association between decreased cognitive functioning and incident IADL limitations. Physical inactivity was associated with an increased risk of incidence IADL limitations even among the cognitively impaired. In addition to our work examining the impact of individual-level factors on incident I/ADL limitations, we have also explored whether family-level modifiers influence the onset of I/ADL limitations. We observed that contacts with friends may be particularly beneficial against incident I/ADL limitations for those with cognitive impairment. These findings have critical importance for clinicians, patients, and family members of individuals with cognitive impairments or incipient dementia. By managing conventional risk factors and maintain social contacts with friends, it may be possible to stave off dependencies, maximize quality of life, and minimize caregiver burden.

Disseminating these results is particularly important because conventional risk factors for ADL limitations like depression are often undertreated among those with cognitive impairment.(*2*) Even traditional vascular risk factors like high blood pressure, dyslipidemia, diabetes mellitus, smoking and atherosclerotic disease may be untreated in those with cognitive impairment. A study of patients with Alzheimer's disease without cerebrovascular disease but with at least one vascular risk factor found that 25.7% of patients had no vascular risk factors treated and 42.5% had only some risk factor treated.(*10*) However, maintaining healthy risk factor profiles may help individuals with incipient dementia to maintain functional independence, and thereby lower their risk for institutionalization and decrease care-giver burden.

While the present report describes the impact of individual-level and family-level modifiers on the association between cognitive impairment and functional limitations, there are many other neighborhood-level factors that have not yet been explored. It is important to explore these factors because they may offer new ways of breaking the link between cognitive impairments and functional limitations. The findings have the potential to substantially improve the quality of life of adults with memory impairments, reduce caregiving demands for family members, and delay institutionalization. This is especially important for older veterans and those with prior exposure to mild, moderate, or severe TBI, who are at elevated risk of memory loss and dementia. As the number of warfighters surviving TBI or other causes of cognitive impairment grows, it is crucial to identify the resources and tools that provide the greatest benefit to those individuals. Findings from this research can help provide guidance to individuals and families as well as clinicians, military planners, and policy makers.

REFERENCES

1. M. Luppa, T. Luck, E. Brahler, H. H. Konig, S. G. Riedel-Heller, Prediction of institutionalisation in dementia. A systematic review. *Dementia and geriatric cognitive disorders* **26**, 65 (2008).
2. P. Dorenlot, M. Harboun, V. Bige, J. C. Henrard, J. Ankri, Major depression as a risk factor for early institutionalization of dementia patients living in the community. *International journal of geriatric psychiatry* **20**, 471 (May, 2005).
3. A. M. Jette, Toward a common language for function, disability, and health. *Physical therapy* **86**, 726 (May, 2006).
4. L. M. Verbrugge, A. M. Jette, The disablement process. *Social science & medicine* **38**, 1 (Jan, 1994).
5. Q. Wu *et al.*, Combining Direct and Proxy Assessments to Reduce Attrition Bias in a Longitudinal Study. *Alzheimer disease and associated disorders*, (Sep 18, 2012).
6. V. Njegovan, M. M. Hing, S. L. Mitchell, F. J. Molnar, The hierarchy of functional loss associated with cognitive decline in older persons. *The journals of gerontology. Series A, Biological sciences and medical sciences* **56**, M638 (Oct, 2001).
7. P. Huber, in *Proceedings of the Fifth Berkeley Symposium on Mathematical Statistics and Probability* L. LeCam, J. Neyman, Eds. (University of California Press, 1967), pp. 221-233.
8. P. St. Clair *et al.*, “RAND HRS Data Documentation” (RAND Center for the Study of Aging, Santa Monica, CA, 2010).
9. M. A. Hernan, B. Brumback, J. M. Robins, Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. *Epidemiology* **11**, 561 (Sep, 2000).
10. Y. Deschaintre, F. Richard, D. Leys, F. Pasquier, Treatment of vascular risk factors is associated with slower decline in Alzheimer disease. *Neurology* **73**, 674 (Sep 1, 2009).

APPENDICES: Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, study questionnaires, and surveys, etc.

Abstract for the American Academy of Neurology Annual Meeting in Philadelphia, PA April 26-May 3, 2014

Title: Forgetful but not disabled: Predictors of incident IADL limitations

Authors: Pamela M. Rist, ScD, Jessica R. Marden, MPH, Benjamin D. Capistrant, ScD, Qiong Wu, PhD, M. Maria Glymour, ScD

Abstract Body

Objective: To examine whether the impact of memory on incident instrumental activities of daily living (IADLs) limitations is exacerbated by smoking and depression.

Background: Cognitive impairment predicts limitations in IADLs, but it is not known whether individual-level factors modify this association.

Design/Methods: We followed 5219 Health and Retirement Study participants aged 65+ with memory function measures and without activity limitations in 1998 or 2000 biennially for 12 years. Hypothesized modifiers included smoking and depression. Memory was categorized into four quartiles (low, mild, moderate, and high memory function) and used to predict IADL limitation count with Poisson regression. We included interaction terms between memory category and smoking and depression, in separate models; we estimated relative and absolute effects.

Results: Low memory predicted risk of IADL limitations (RR=2.40; 95% CI: 1.54-3.74) compared to high memory score. Neither smoking (RR=1.94; 95% CI: 0.73-5.81) nor depression (RR=1.89; 95% CI: 0.93-3.82) in the prior wave were significantly associated with incident IADL limitations. Interaction terms between smoking and memory suggested stronger relative effects amongst those with high memory but the interactions were not statistically significant (all p-values>0.29). On an absolute scale, smoking predicted 0.13 additional incident IADLs for those with high memory but only 0.06 for those with low memory. Similarly, interaction terms between depression and memory suggested stronger relative effects amongst those with high memory,but were not statistically significant. On an absolute scale, depression predicted 0.11 additional incident IADL limitations for those with high memory and 0.05 additional incident IADL limitations for those with low memory.

Conclusion: Smoking and depression did not show larger relative effects among those with normal memory than among cognitively impaired. It may be difficult to use individual-level modifiers to ameliorate impacts of memory impairment on incident IADL limitations.

Funding: This work is supported by the Telemedicine and Advanced Technology Research Center at the U.S. Army Medical Research and Materiel Command through award W81XWH-12-1-0143.

Abstract for Society of Epidemiology Annual Conference in Seattle, WA June 24-27, 2014

Title: From forgetful to disabled: Does physical inactivity accelerate onset of IADL limitations for memory impaired adults?

Authors: P. M. Rist, J.R. Marden, B. D. Capistrant, Q. Wu, and M. M. Glymour (Harvard School of Public Health, Boston, MA 02115)

Abstract Body

Physical inactivity predicts onset of disability in cognitively healthy older adults, but it is not known whether physical inactivity also predicts onset of functional dependence for individuals with memory loss. We examined whether physical inactivity was associated with incident limitations in Instrumental Activities of Daily Living (IADLs) among individuals with impaired memory and whether the association between physical inactivity and IADL limitations was modified by memory. We followed 5219 Health and Retirement Study participants aged 65+ with memory function measures and without activity limitations at baseline biennially for 12 years. Memory, categorized into 4 groups based on quartile cutpoints of the baseline memory score, was used to predict IADL limitation count with Poisson regression and inverse probability weights to adjust for time-varying confounders and attrition. We estimated relative (risk ratio (RR)) and absolute effects (number of additional limitations) from models including memory, physical inactivity, and interaction terms between memory and physical inactivity. The highest quartile of memory functioning predicted decreased risk of IADL limitations (RR=0.23; 95% CI: 0.13-0.41) compared to the lowest quartile of memory functioning. Physical inactivity (RR=1.47; 95% CI: 1.12-1.95) in the prior wave predicted incident IADL limitations among those with low memory functioning. The interaction term between physical inactivity and high memory suggested stronger relative effects among those with high memory, but was not statistically significant. On an absolute scale, physical inactivity predicted 0.12 additional incident IADL limitations for those with high memory (p-value for difference in absolute effects for physically active compared to inactive=0.01) and also for those with low memory (p-value=0.01). Physical inactivity appears to have similar relative and absolute effects among those with high and low memory functioning.

Funding: This work is/was supported by the Telemedicine and Advanced Technology Research Center (TATRC) at the U.S. Army Medical Research and Materiel Command (USAMRMC) through award W81XWH-12-1-0143.

SUPPORTING DATA: All figures and/or tables shall include legends and be clearly marked with figure/table numbers.

Table 1. Baseline Characteristics of Those Included in the Analysis of Memory Category and Any Incident ADL Limitation by Memory Impairment Category at Baseline.

Characteristic	Memory Impairment Category at Baseline			
	Best Memory (N= 1369)	Moderate Memory (N= 1348)	Poor Memory (N= 1285)	Worst Memory (N= 1217)
Age (mean, std)	70.1 (4.5)	70.7 (4.7)	73.1 (5.1)	77.9 (6.0)
Gender (% male)	20.6	42.9	51.1	56.2
Race (% black)	0.7	2.9	11.8	24.7
Southern birthplace (%)	9.4	10.2	15.6	18.2
Years of education (mean, std)	13.3 (2.4)	12.9 (2.6)	12.4 (2.8)	11.2 (3.3)
Mother had ≥8 years of education (%)	58.4	52.5	51.2	44.0
Father had ≥8 years of education (%)	49.9	42.9	43.9	40.4
Marital status				
Married (%)	65.2	70.0	65.6	53.5
Divorced/separated (%)	8.1	5.3	5.4	5.8
Widowed (%)	23.7	20.7	25.7	37.0
Never married (%)	3.0	4.0	3.4	3.8
Physically inactive (%)	48.5	49.8	54.3	65.6
Not drinking (%)	69.3	68.3	74.2	77.2
Current smoking (%)	9.9	10.4	7.9	6.8
Current depression (%)	8.7	9.1	10.7	13.5
Low household-size adjusted income (%)	12.9	14.9	20.6	31.2
Body mass index (mean, std)	26.1 (4.5)	26.7 (4.6)	26.6 (4.4)	26.0 (4.1)
Number of comorbidities (mean, std)	1.4 (1.1)	1.6 (1.2)	1.7 (1.2)	1.7 (1.2)

Table 2. Distribution of Memory Categories and Total Number of People Reporting Incident IADL Limitations by Year.

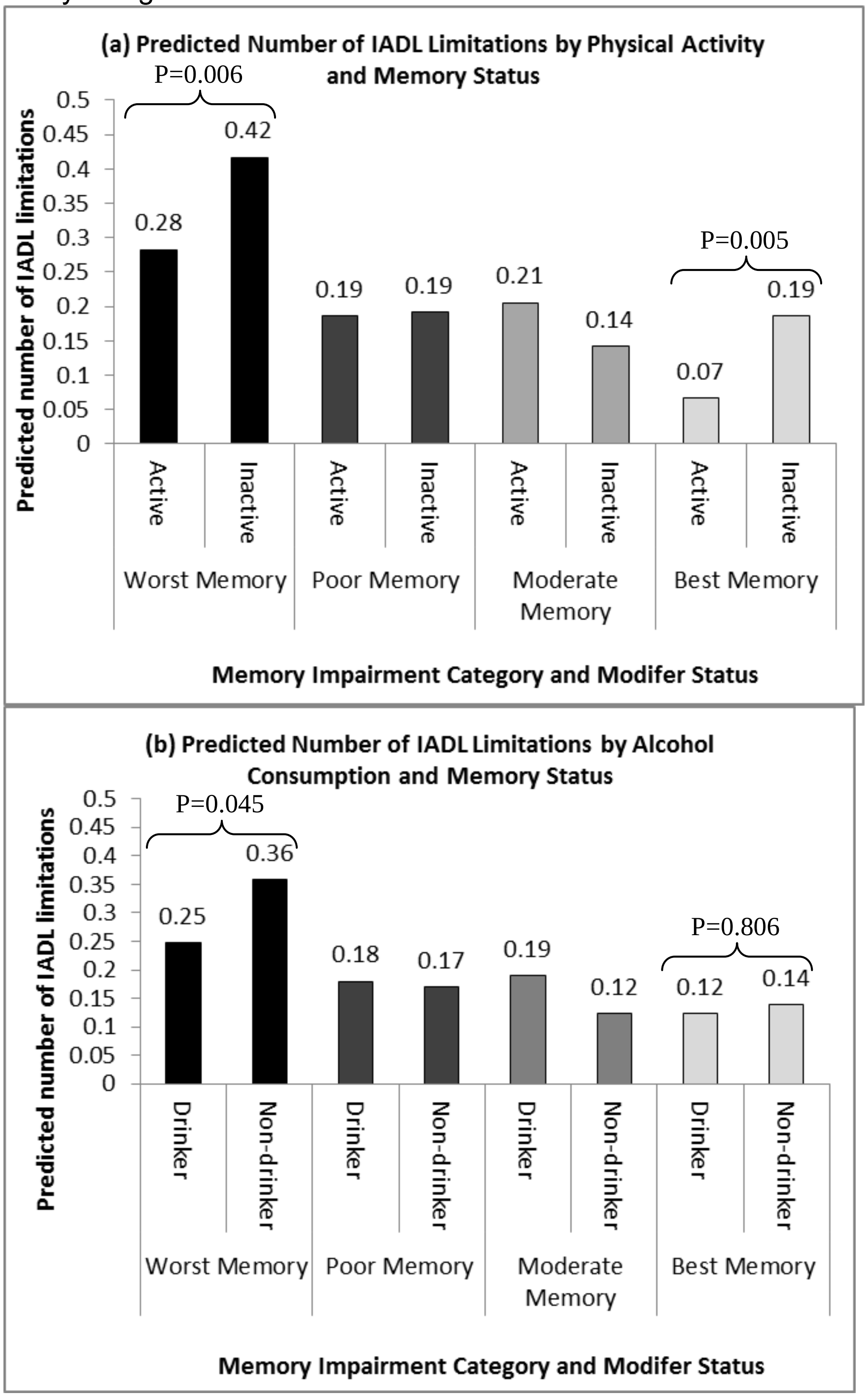
	Year						
Memory Category	2002	2004	2006	2008	2010	Number of people reporting Incident IADL Limitations (n)	Mean number of limitations reported among those reporting limitations (n, std)
High memory (n, %)	1369 (26.2)	1012 (23.8)	659 (19.4)	468 (17.2)	326 (15.4)	189	1.64 (1.13)
Moderate memory (n, %)	1348 (25.8)	1037 (24.4)	767 (22.6)	593 (21.8)	407 (19.2)	268	1.49 (0.94)
Poor memory (n, %)	1285 (24.7)	1113 (26.2)	984 (29.0)	746 (27.4)	624 (29.5)	478	1.63 (1.11)
Worst memory (n, %)	1217 (23.3)	1082 (25.5)	988 (29.1)	919 (33.7)	761 (35.9)	1116	2.18 (1.42)
Number of people reporting IADL Limitations (n)	524	514	398	290	325	2051	
Mean number of limitations reported (n, std)	1.90 (1.29)	1.82 (1.25)	1.88 (1.30)	1.92 (1.27)	2.12 (1.45)		1.91 (1.31)

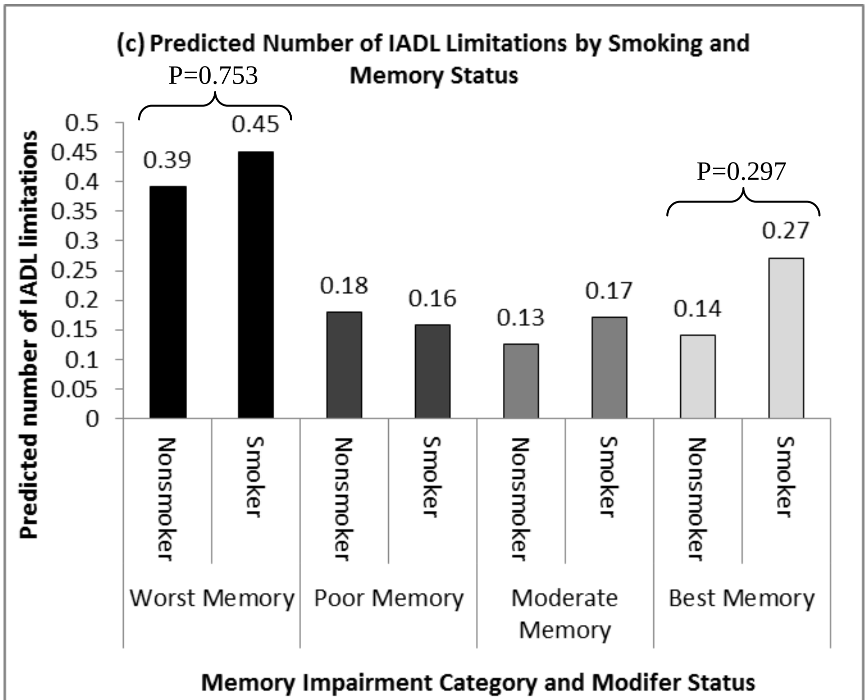
List of abbreviations: IADL = instrumental activities of daily living; std = standard deviation

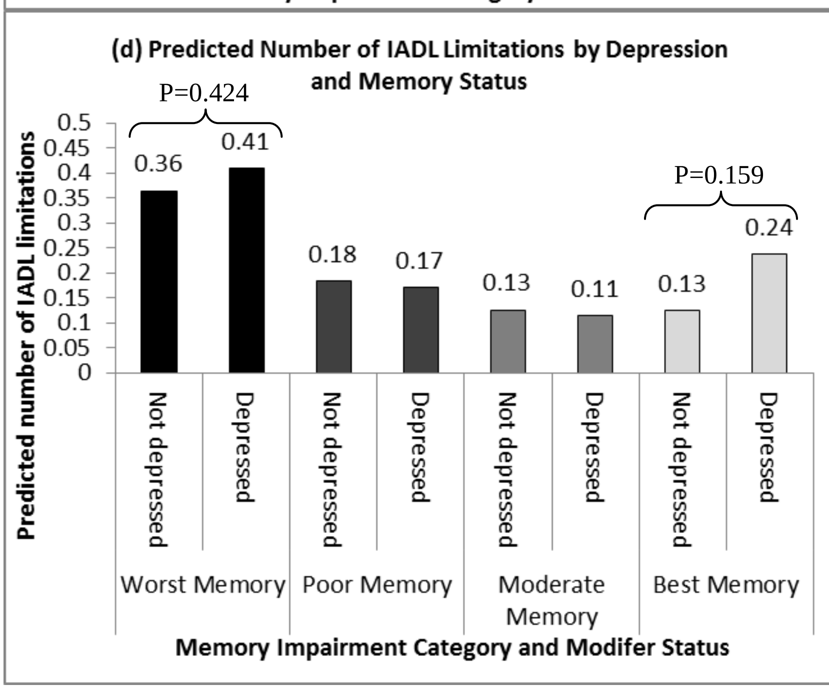
Table 3. Association between Memory Category and Incident IADL Limitations Including Interactions between Memory Impairment and Individual Health Factors.

	OR	95%	CI
Physical Activity			
Best Memory	0.23	0.13	0.41
Best Memory*No Physical activity	0.73	0.28	1.89
Moderate Memory	0.66	0.44	0.98
Moderate Memory*No Physical activity	1.91	0.98	3.74
Poor Memory	0.47	0.18	1.25
Poor Memory *No Physical activity	0.70	0.42	1.17
No Physical Activity	1.47	1.12	1.95
Drinking			
Best Memory	0.49	0.17	1.42
Best Memory*Not Drinking	0.77	0.32	1.82
Moderate Memory	0.73	0.41	1.27
Moderate Memory*Not Drinking	0.78	0.26	2.40
Poor Memory	0.45	0.18	1.10
Poor Memory*Not Drinking	0.66	0.36	1.20
Not Drinking	1.44	0.96	2.16
Smoking			
Best Memory	0.36	0.21	0.60
Best Memory*Smoking	0.32	0.24	0.43
Moderate Memory	0.46	0.37	0.57
Moderate Memory*Smoking	1.68	0.47	6.02
Poor Memory	1.17	0.28	4.87
Poor Memory*Smoking	0.76	0.20	2.96
Smoking	1.15	0.50	2.65
Depression			
Best Memory	0.35	0.24	0.50
Best Memory*Depression	0.35	0.26	0.46
Moderate Memory	0.50	0.40	0.63
Moderate Memory *Depression	1.68	0.79	3.61
Poor Memory	0.81	0.40	1.63
Poor Memory*Depression	0.83	0.40	1.70
Depression	1.12	0.85	1.48

Figure 1. Predicted number of incident IADL limitation per wave, by modifier and memory status, with statistical significance tests for differences in absolute effects for those in the worst and best memory categories.







Legend: IADL limitations were assessed each wave (every two years). We adjusted for the following potential time-constant confounders: age, age squared, sex, race, southern birthplace, education, mother's and father's educations, and height. Additionally, we adjusted for the following time-varying confounders using an inverse probability weighting approach: marital status, log of household size-adjusted wealth, body mass index, a summary score of self-reported comorbidities, and our modifiers.

Table 4. Characteristics of Those Included in the Analysis of Memory Category and Any Incident ADL Limitation by Memory Impairment Category at first exposure wave.

Characteristic	Poor Memory (N=1025)	Normal Memory (N=3075)
Age (mean, std)	77.5 (5.9)	71.0 (4.8)
Gender (% male)	57.1	39.0
Race (% black)	24.9	3.9
Southern birthplace (%)	17.3	11.7
Years of education (mean, std)	11.4 (3.3)	12.9 (2.5)
Mother had ≥8 years of education (%)	45.9	54.7
Father had ≥8 years of education (%)	40.5	47.1
Physically inactive (%)	55.7	48.2
Not drinking moderately (%)	77.9	71.4
Current smoking (%)	7.2	10.9
Current depression (%)	10.1	7.5
Low household-size adjusted income (%)	28.7	15.4
Body mass index (mean, std)	25.9 (4.0)	26.2 (4.2)
Number of comorbidities (mean, std)	1.6 (1.1)	1.5 (1.1)
Living arrangement		
Live with spouse	55.3	66.3
Live with someone other than spouse	11.2	8.1
Live alone	33.5	25.5
Proximity to children		
Live with children	15.9	14.3
No children	8.1	7.4
Children within 10 miles	45.0	45.2
Children over 10 miles	31.0	33.1
Less than weekly contact with friends	41.2	39.2
Spouse's employment status		
Retired	36.6	41.2
Full time	1.9	6.2
Part time	5.7	11.2
Not working/disabled	11.2	7.8
No spouse	44.7	33.7
Spouse's depression status		
Not depressed	47.6	62.3
Depressed	7.7	4.1
No spouse	44.7	33.7
Spouse's educational status		
High school diploma/GED	34.0	39.9
College diploma or higher	7.3	15.3
Less than a high school diploma/GED	14.1	11.2
No spouse	44.7	33.7

Table 5. Association between family-level variables and risk of incident ADL and IADL limitations.

	ADL			IADL		
	OR	**95%**	**CI**	**OR**	**95%**	**CI**
Living Arrangement						
Live with spouse	1.00			1.00		
Live with someone other than spouse	1.20	0.96	1.50	1.07	0.85	1.36
Live Alone	1.00	0.87	1.17	0.89	0.77	1.03
Proximity to Children						
Live with children	1.00			1.00		
No children	1.07	0.82	1.39	0.88	0.66	1.16
Children within 10 miles	0.89	0.74	1.07	0.97	0.80	1.17
Children over 10 miles	0.94	0.78	1.15	0.97	0.79	1.18
Contacts with friends						
Weekly or more frequent contact	1.00			1.00		
Less than weekly contact	1.01	0.89	1.14	1.01	0.89	1.14
Spouse's employment status						
Retired	1.00			1.00		
Employed full time	1.09	0.72	1.64	1.05	0.70	1.59
Employed part time	0.98	0.77	1.23	0.99	0.78	1.25
Not working	0.97	0.77	1.23	1.20	0.94	1.52
No spouse	1.04	0.89	1.21	0.90	0.78	1.04
Spouse's depression status						
Not depressed	1.00			1.00		
Depressed	1.37	1.03	1.82	1.12	0.81	1.55
No spouse	1.07	0.93	1.24	0.93	0.80	1.07
Spouse's educational status						
High school education	1.00			1.00		
College education	0.91	0.72	1.13	0.96	0.77	1.19
Less than high school education	0.76	0.62	0.94	1.24	1.00	1.54
No spouse	1.14	0.96	1.34	0.87	0.74	1.03

Table 6. Association between memory category and incident IADL limitations including interactions between memory impairment and individual health factors.*

	ADL			IADL		
	OR	**95%**	**CI**	**OR**	**95%**	**CI**
Living Arrangement						
Good memory	0.52	0.35	0.77	0.32	0.22	0.46
Live with someone other than spouse	1.36	0.80	2.32	1.42	0.80	2.52
Good memory*Live with someone other than spouse	0.63	0.28	1.39	0.74	0.32	1.74
Live Alone	1.08	0.71	1.64	0.94	0.64	1.37
Good memory*Live Alone	1.00	0.55	1.80	1.37	0.76	2.48
Proximity to Children						
Good memory	0.22	0.07	0.65	0.22	0.05	0.93
No children	0.26	0.03	2.41	0.07	0.01	0.43
Good memory*No children	7.60	0.60	95.72	6.14	0.27	138.32
Children within 10 miles	0.55	0.25	1.18	1.26	0.45	3.51
Good memory*Children within 10 miles	0.83	0.21	3.22	0.55	0.11	2.66
Children over 10 miles	0.50	0.23	1.08	0.74	0.29	1.91
Good memory*Children over 10 miles	1.57	0.42	5.89	0.80	0.16	4.03
Contacts with friends						
Good memory	0.59	0.45	0.77	0.41	0.32	0.54
Less than weekly contact	1.28	0.99	1.67	1.24	0.96	1.59
Good memory*Less than weekly contact	0.78	0.51	1.18	1.02	0.66	1.57
Spouse's employment status						
Good memory	0.55	0.40	0.77	0.35	0.25	0.49
Full time	1.57	0.63	3.89	0.92	0.37	2.32
Good memory*Full time	0.57	0.13	2.49	1.09	0.24	4.85
Part time	0.83	0.47	1.48	0.77	0.44	1.36
Good memory*Part time	1.03	0.48	2.22	1.30	0.58	2.91
Not working	1.11	0.71	1.73	0.85	0.59	1.23
Good memory*not working	1.05	0.54	2.01	0.89	0.44	1.81
No spouse	0.82	0.61	1.09	0.65	0.49	0.86
Good memory*No spouse	1.02	0.67	1.53	1.04	0.69	1.58
Spouse's depression status						
Good memory	0.58	0.39	0.86	0.40	0.27	0.58
Depressed	1.53	0.81	2.89	1.29	0.66	2.52
Good memory*Depressed	0.55	0.24	1.31	0.79	0.31	2.05
No spouse	1.11	0.75	1.64	0.99	0.70	1.42
Good memory*No spouse	0.76	0.46	1.26	0.88	0.52	1.50
Spouse's educational status						
Good memory	0.59	0.41	0.84	0.38	0.27	0.55
College education	0.87	0.53	1.40	1.34	0.88	2.05
Good memory*College education	1.23	0.61	2.48	0.69	0.35	1.35

Less than high school education	1.42	0.97	2.08	0.71	0.49	1.05
Good memory*Less than high school education	0.71	0.36	1.38	1.13	0.53	2.37
No spouse	0.79	0.57	1.08	0.58	0.43	0.79
Good memory*No spouse	1.01	0.64	1.59	1.00	0.64	1.57

*Good memory is defined as memory score higher than the 25th percentile of the memory score distribution at baseline. The reference group for the living arrangement analysis is living with spouse. The reference group for the proximity to children analysis is living with children. The reference group for the contacts with friends analysis is more than weekly contact. The reference group for the spouse's employment status is having a spouse who is retired. The reference group for spouse's depression status is having a spouse who is not depressed. The reference group for spouse's educational status is having a spouse with a high school education.

Dementia and dependence

Do modifiable risk factors delay disability?

Pamela M. Rist, ScD
Benjamin D. Capistrant, ScD
Qiong Wu, PhD
Jessica R. Marden, MPH
M. Maria Glymour, ScD

Correspondence to Dr. Rist: prist@mail.harvard.edu

ABSTRACT

Objective: To identify modifying factors that preserve functional independence among individuals at high dementia risk.

Methods: Health and Retirement Study participants aged 65 years or older without baseline activities of daily living (ADL) limitations (n = 4,922) were interviewed biennially for up to 12 years. Dementia probability, estimated from direct and proxy cognitive assessments, was categorized as low (i.e., normal cognitive function), mild, moderate, or high risk (i.e., very impaired) and used to predict incident ADL limitations (censoring after limitation onset). We assessed multiplicative and additive interactions of dementia category with modifiers (previously self-reported physical activity, smoking, alcohol consumption, depression, and income) in predicting incident limitations.

Results: Smoking, not drinking, and income predicted incident ADL limitations and had larger absolute effects on ADL onset among individuals with high dementia probability than among cognitively normal individuals. Smoking increased the 2-year risk of ADL limitations onset from 9.9% to 14.9% among the lowest dementia probability category and from 32.6% to 42.7% among the highest dementia probability category. Not drinking increased the 2-year risk of ADL limitations onset by 2.1 percentage points among the lowest dementia probability category and 13.2 percentage points among the highest dementia probability category. Low income increased the 2-year risk of ADL limitations onset by 0.4% among the lowest dementia probability category and 12.9% among the highest dementia probability category.

Conclusions: Smoking, not drinking, and low income predict incident dependence even in the context of cognitive impairment. Regardless of cognitive status, reducing these risk factors may improve functional outcomes and delay institutionalization. *Neurology®* 2014;82:1543–1550

GLOSSARY

ADL = activities of daily living; **CI** = confidence interval; ***DSM-III-R*** = *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition, revised; ***DSM-IV*** = *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; **HRS** = Health and Retirement Study; **IPW** = inverse probability weighting; **OR** = odds ratio.

Cognitive impairment causes losses in independence in daily activities,[1] which hasten institutionalization.[2] Little prior research has examined whether factors that delay disability in cognitively normal adults have similar benefits among the cognitively impaired.

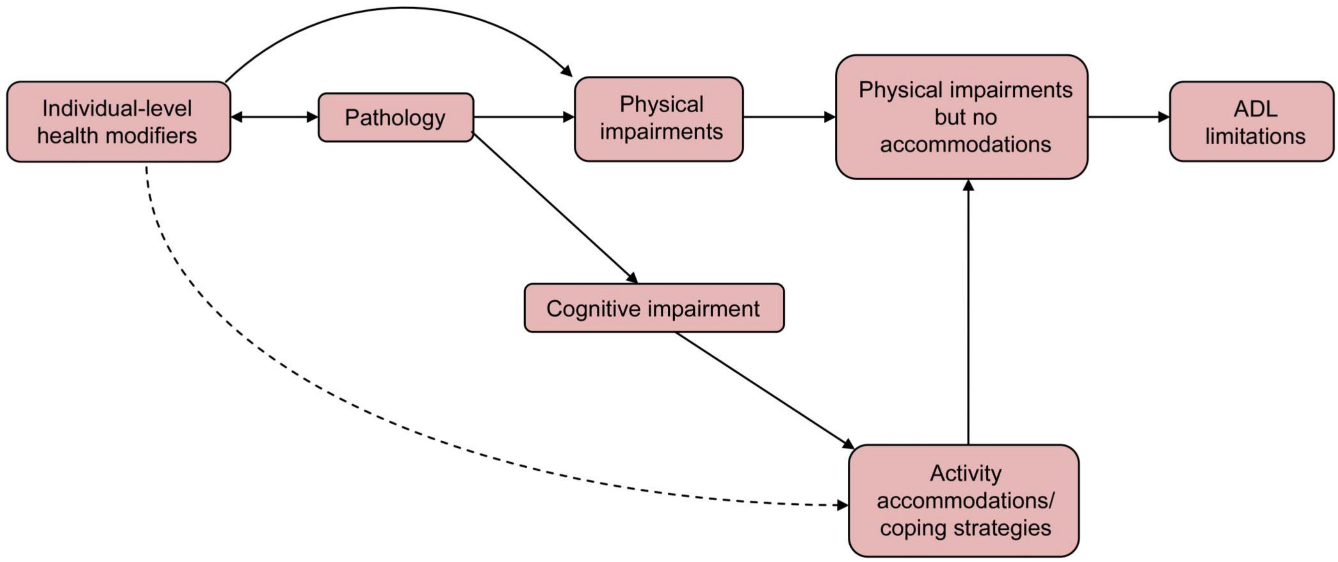
We hypothesized that onset of impairments in functional independence among individuals with cognitive impairment may be substantially accelerated by modifiable individual risk factors. This hypothesis is rooted in understanding of disability as emerging when physical impairments in body functioning or structure occur and it is not possible to adopt environmental, behavioral, and instrumental accommodations to overcome these impairments (see figure 1).[3,4] Individual-level modifiers, such as physical inactivity, alcohol consumption, smoking, depression, and low household income, may influence both the development of physical impairments and patients' ability to use accommodations or coping strategies. Cognitive impairment may also affect basic activities of daily living (ADL) independence because it reduces the patient's ability to adopt accommodations

Supplemental data at Neurology.org

From the Division of Preventive Medicine (P.M.R.), Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston; Departments of Social and Behavioral Sciences (P.M.R., J.R.M., M.M.G.) and Epidemiology (P.M.R.), Harvard School of Public Health, Boston, MA; Carolina Population Center (B.D.C.), University of North Carolina–Chapel Hill; Institute of Social Science Survey (Q.W.), Peking University, Beijing, China; and the Department of Epidemiology & Biostatistics (M.M.G.), University of California, San Francisco.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Figure 1 **Hypothesized influence of individual-level health modifiers and cognitive impairment on the disablement process**



An adaptation of the disablement process model by Verbrugge and Jette,[4] this figure illustrates how the co-occurrence of illness pathology and cognitive impairment leads to functional limitations and disability by impairing the patient's ability to adopt accommodations and coping strategies. ADL = activities of daily living.

or coping strategies. The combination of individual modifying risk factors and cognitive status will determine whether the patient is able to successfully use activity accommodations to interrupt the translation of physical impairments into ADL limitations. Assessing whether these individual risk factors modify the translation of cognitive impairments into disability has clinical importance because many of these factors may be insufficiently managed among patients with dementia.[5]

METHODS The Health and Retirement Study (HRS) is a nationally representative longitudinal survey of Americans aged 50 years or older and their spouses.[6,7] Participants were enrolled in 1992, 1993, and 1998 and were interviewed biannually through 2010.

Standard protocol approvals, registrations, and patient consents. The HRS was approved by the University of Michigan Health Sciences Human Subjects Committee. These analyses were determined exempt by the Harvard School of Public Health Office of Human Research Administration.

Outcome assessment. The outcome for this study was self-reported or proxy-reported (approximately 4% per wave) difficulty in 5 ADL (getting across a room, dressing, bathing, eating, and getting in and out of bed) in the past 30 days. Possible response options were yes, no, or do not do, which was treated as missing in this analysis. We looked at each activity individually and also used an indicator for any activity limitation, capturing limitations in any of the 5 ADL (based on the RAND HRS coding[8]).

Exposure status. Our primary exposure was imputed dementia probability score, a measure of cognitive impairment. Methods for calculating this score have been described in detail elsewhere.[9] Briefly, for participants too impaired to participate in interviews (approximately 2% per wave), proxies completed the Jorm Informant Questionnaire for Cognitive Decline and a single-item memory impairment question. Respondents able to participate in interviews completed immediate and delayed recall of 10-word lists and a modified Telephone Interview for Cognitive Status. In a subsample of participants, these items were combined and calibrated against dementia diagnosis according to *DSM-III-R* and *DSM-IV* criteria (C statistic = 94.3%). The dementia probability score corresponds to the estimated probability that the individual had dementia at interview per this calibration. For our analyses, the dementia probability score was divided into 4 categories (0 to $\leq$0.25, 0.25 to $\leq$0.50, 0.50 to $\leq$0.75, and 0.75 to $\leq$1), which represent low, mild, moderate, and high probability of developing dementia. The category of 0 to $\leq$0.25 (normal cognitive function) was used as the reference group for all analyses. In our longitudinal analyses, dementia probability score was assessed in the wave before ADL outcome assessment.

In secondary analyses, we used an imputed memory score as our measure of cognitive impairment and observed similar results (see appendix e-1 on the *Neurology*® Web site at Neurology.org).

Assessment of individual-level modifiers. We were interested in determining whether 5 self-reported or proxy-reported (approximately 2% per wave) individual-level factors (physical activity, drinking alcohol, smoking, depression, and income) predict similar reductions in the risk of incident ADL limitations regardless of level of cognitive impairment. Furthermore, we wanted to know whether these factors ameliorate or exacerbate the effects of cognitive impairment on incident ADL limitations, i.e., whether they interact with the cognitive impairment measures in predicting incident ADL limitations. Because of changes in the assessment of physical activity levels over time, physical activity was dichotomized as active vs inactive with active defined as vigorous activity $\geq$3 times per week in 1998 to 2002 and >1 time per week from 2004 onward (the closest available category to the previously used $\geq$3 times per week cutpoint). Alcohol consumption was dichotomized into moderate drinking (more than 0 but fewer than 2 drinks per day) vs not drinking. Because of the low number of participants consuming 2 or more drinks per day, we excluded these individuals from our analyses of alcohol consumption, dementia category, and incident ADL limitations. Sensitivity analyses contrasting moderate drinkers with nonmoderate drinkers (nondrinkers or heavy drinkers) showed similar results to those presented here. Current smoking status was dichotomized (yes/no). An indicator variable for depression was constructed based on reporting ≥3 depressive symptoms on a modified 8-item Centers for Epidemiologic Studies–Depression Scale in the past 2 weeks. This threshold has been shown to have high sensitivity (71%) and specificity (79%) for depression per the Composite International Diagnostic Interview–Short Form.[10] We constructed an indicator variable for low income using a cutpoint of $12,031 (based on the 25th percentile of the household size–adjusted income at baseline). Modifier information was assessed in the wave before outcome assessment.

Covariates. We adjusted for the following potential time-constant confounders: age (centered, continuous), age squared, sex, race (black vs other), southern birthplace, education (modeled as linear terms for years of education with discontinuities at completion of high school and completion of college plus an indicator variable for GED completion), mother's and father's education (≤8 years vs >8 years), and height (sex-specific baseline quartiles). In addition, we adjusted for the following time-varying confounders: marital status (divorced/separated, widowed, never married, married), log of household size–adjusted wealth (continuous), body mass index (continuous), self-reported comorbidities (yes/no indicators for high blood pressure, diabetes, cancer, lung disease, heart disease, stroke, psychiatric problems, and arthritis), interview wave, and our modifiers. Time-constant confounders were assessed at study baseline (1998) and time-updated confounders were assessed at the wave before the exposure. Those missing information on any covariates at baseline were excluded from our analyses. If the covariate was missing during follow-up, the last reported value was carried forward.

Statistical analysis. Pooled logistic regression models were used to calculate odds ratios (ORs), which with rare outcomes approximates a hazard ratio as in continuous time survival analyses. The relationship of the dementia probability categories with risk of ADL limitations was approximately linear, so the categories were treated as a linear variable. Participants were censored from analysis after last interview, onset of activity limitations, death, or at first wave of missing information on dementia probability. We used inverse probability weighting (IPW) to adjust for potential time-varying confounding. IPW required one wave of "run-in" (see below), so our first "exposure" wave was in 2000 and our first "outcome" wave was in 2002. Those who reported ADL limitations in 1998 or 2000 were excluded from our analyses.

To assess whether any of our modifiers ameliorated or exacerbated the effects of dementia score on ADL limitations, 2 different approaches were used. First, we included an interaction term between dementia score category and each modifier (in separate models for each modifier) to test whether each modifier had different relative effects on ADL limitations depending on the participant's dementia score. Next, to compare the absolute effects of each modifier in participants with highest or lowest dementia score, we calculated the marginal probability of developing an activity limitation according to modifier status and dementia category. If effects of any risk factor are precisely multiplicative, the absolute benefit for individuals with cognitive impairment will be larger. These probabilities were calculated using the coefficients estimated in the logistic models with interaction terms and the actual population distribution of other covariates. The marginal probabilities were then compared based on the predicted population incidence rate of ADL limitations if everyone in the population had: (1) low dementia probability and the "beneficial" value of the modifier; (2) low dementia probability and the "adverse" value of the modifier; (3) high dementia probability and the "beneficial" value of the modifier; or (4) high dementia probability and the "adverse" value of the modifier. All analyses were performed using PROC SURVEYLOGISTIC in SAS 9.2 (SAS Institute, Cary, NC) and Stata 12 (StataCorp, College Station, TX) with weights as described below.

We used IPW to avoid introducing bias by adjusting for variables potentially affected by prior exposure but which affect future exposure. We constructed 4 weights: "treatment" (category of dementia score), modifier status (separate weights were calculated for each modifier), survival, and participation in HRS. These weights were multiplied to create a weight for each observation reflecting the inverse probability that the individual was alive and participated in the outcome wave, and had the dementia and modifier values he or she actually had, given past dementia, modifier, and covariate history. We additionally included the HRS sampling weight from 1998. Weights were stabilized[11] and truncated at the 98th percentile to minimize the influence of outliers.

We had 4,922 individuals eligible for our analysis of the association between dementia score and any ADL limitation (see figure e-1 for exclusions). For analyses of onset of specific ADL limitations, the exact number of individuals eligible differs slightly for each ADL because of differences in the baseline prevalence of each ADL limitation.

RESULTS Most respondents (94.2%) had low dementia probability at baseline (table 1) and throughout follow-up (table 2).

Higher dementia probability score category was associated with increased risk of incident ADL limitations, with a per-category OR of 1.65 (95% confidence interval [CI]: 1.49, 1.83) (results not shown). This implies that individuals with the highest dementia category (>75% probability of dementia) had 4.48 times the odds of onset of ADL limitations as individuals in the lowest dementia category (≤25% probability of dementia).

Table 3 shows the association between dementia probability category and risk of incident ADL limitations, the association between each modifier and incident ADL limitations, and the interaction coefficient between dementia probability and each modifier. In these models, an interaction coefficient of 1 indicates that the modifier has the same relative effect on ADL limitations regardless of dementia probability; if the interaction coefficient is less than 1, it indicates that the modifier effect is lower (less harmful) among those with higher dementia probability.

For the outcome of any ADL limitation, among the physically active, each unit increase in dementia

Table 1 Baseline characteristics of participants included in the analysis of dementia probability category and any incident activities of daily living limitations by dementia probability category at baseline

	Dementia probability category			
	0–0.25 (n = 4,636)	0.25–0.50 (n = 146)	0.50–0.75 (n = 65)	0.75–1 (n = 75)
Age, y, mean (SD)	72.4 (5.6)	80.0 (6.8)	81.2 (6.0)	80.6 (6.7)
Sex, % male	43.7	41.8	29.2	22.7
Race, % black	9.1	19.9	15.4	24.0
Southern birthplace, %	12.7	20.6	15.4	22.6
Years of education, mean (SD)	12.6 (2.8)	10.8 (3.5)	9.9 (3.4)	9.9 (3.9)
Mother had ≥8 y of education, %	53.0	45.9	36.9	33.3
Father had ≥8 y of education, %	45.5	41.1	30.8	33.3
Height, m, mean (SD)	1.7 (0.1)	1.7 (0.1)	1.6 (0.1)	1.6 (0.1)
Marital status, %				
Married	65.5	48.0	40.0	41.3
Divorced/separated	6.3	5.5	9.2	5.3
Widowed	24.7	43.2	49.2	52.0
Never married	3.5	3.4	1.5	1.3
Not physically active, %	51.3	63.7	69.2	84.0
Nondrinker, %	74.8	87.1	92.2	94.7
Current smoking, %	8.9	10.3	1.5	4.0
Current depression, %	9.3	19.2	13.9	17.3
Low household size-adjusted income, %	18.4	39.0	50.8	50.7
Body mass index, kg/m^2, mean (SD)	26.1 (4.2)	25.4 (4.0)	24.2 (4.4)	24.4 (4.0)
No. of comorbidities, mean (SD)	1.5 (1.2)	1.6 (1.1)	1.6 (1.3)	1.4 (1.2)

category was associated with an OR of 1.83 (95% CI: 1.36, 2.46). Low physical activity was associated with an increase in incident ADL limitations among those with the lowest dementia probability OR = 1.51 (95% CI: 1.25, 1.81). The interaction between physical activity and dementia probability was close to 1 and not significant (OR = 0.86; 95% CI: 0.63, 1.18), indicating that the estimated relative harm of low physical activity was similar regardless of dementia category. Depression was also associated with an increased risk of ADL limitations and the interaction between depression and dementia probability suggested that depression may be less harmful, in relative terms, among the cognitively impaired (OR = 0.72; 95% CI: 0.56, 0.92). Not drinking, smoking, and low income were not associated with an increased risk

Table 2 Distribution of dementia probability score and number of any incident ADL limitations by year

	Year					Any incident ADL limitation
	2002	2004	2006	2008	2010	
Dementia probability category, n (%)						
0–0.25	4,636 (94.2)	3,724 (93.7)	3,024 (93.1)	2,379 (92.3)	1,819 (91.8)	1,493 (80.2)
0.25–0.50	146 (3.0)	119 (3.0)	106 (3.3)	105 (4.1)	87 (4.4)	131 (7.0)
0.50–0.75	65 (1.3)	68 (1.7)	54 (1.7)	49 (1.9)	41 (2.1)	92 (4.9)
0.75–1	75 (1.5)	63 (1.6)	66 (2.0)	45 (1.8)	34 (1.7)	145 (7.8)
Any incident ADL limitation, n	536	390	378	298	259	1,861
Died this wave, n	0	255	239	216	205	915
Did not respond, n	0	157	95	78	94	424

Abbreviation: ADL = activities of daily living.
Percentages may not add to 100% because of rounding.

Table 3 Association between dementia category and incident ADL limitations including interactions between dementia category and individual health factors

	Any ADL limitation	Walking	Dressing	Eating	Getting in/out of bed	Bathing
Physical activity						
Dementia category	1.83 (1.36, 2.46)	1.57 (1.16, 2.14)	2.25 (1.70, 2.98)	2.62 (1.93, 3.56)	1.78 (1.32, 2.39)	2.71 (2.08, 3.54)
Dementia × no physical activity	0.86 (0.63, 1.18)	0.96 (0.70, 1.32)	0.71 (0.53, 0.95)	0.68 (0.49, 0.93)	0.90 (0.65, 1.22)	0.64 (0.48, 0.85)
No physical activity	1.51 (1.25, 1.81)	1.51 (1.15, 2.00)	1.69 (1.35, 2.13)	1.98 (1.39, 2.82)	1.78 (1.32, 2.40)	2.22 (1.69, 2.92)
Drinking						
Dementia category	1.27 (0.88, 1.83)	1.58 (1.10, 2.26)	1.41 (0.95, 2.09)	2.01 (1.43, 2.81)	1.67 (1.17, 2.39)	1.90 (1.39, 2.59)
Dementia × not drinking	1.28 (0.87, 1.87)	0.95 (0.65, 1.39)	1.21 (0.81, 1.81)	0.87 (0.61, 1.23)	0.96 (0.67, 1.38)	0.91 (0.66, 1.26)
Not drinking	1.22 (0.96, 1.56)	1.43 (1.04, 1.97)	1.23 (0.92, 1.65)	1.15 (0.77, 1.73)	1.47 (1.00, 2.17)	1.34 (0.97, 1.85)
Smoking						
Dementia category	1.68 (1.51, 1.86)	1.59 (1.43, 1.77)	1.72 (1.53, 1.92)	1.80 (1.59, 2.03)	1.64 (1.45, 1.85)	1.90 (1.72, 2.11)
Dementia category × smoking	0.99 (0.39, 2.54)	0.87 (0.38, 1.99)	0.61 (0.30, 1.25)	0.34 (0.16, 0.72)	0.68 (0.37, 1.27)	0.50 (0.21, 1.22)
Smoking	1.63 (0.94, 2.82)	1.37 (0.69, 2.71)	1.27 (0.66, 2.41)	2.49 (1.21, 5.13)	2.03 (0.97, 4.28)	2.16 (1.19, 3.92)
Depression						
Dementia category	1.71 (1.51, 1.93)	1.62 (1.43, 1.83)	1.78 (1.57, 2.01)	1.99 (1.74, 2.28)	1.67 (1.47, 1.89)	1.94 (1.72, 2.19)
Dementia × depression	0.72 (0.56, 0.92)	0.89 (0.65, 1.22)	0.78 (0.62, 0.98)	0.74 (0.55, 1.00)	1.05 (0.77, 1.42)	0.89 (0.67, 1.19)
Depression	1.59 (1.27, 2.01)	1.69 (1.31, 2.17)	1.54 (1.21, 1.95)	2.65 (1.91, 3.70)	1.53 (1.14, 2.06)	1.47 (1.14, 1.89)
Income						
Dementia category	1.58 (1.36, 1.82)	1.76 (1.52, 2.04)	1.89 (1.63, 2.19)	2.11 (1.75, 2.55)	1.96 (1.65, 2.32)	2.11 (1.82, 2.45)
Dementia × low income	1.24 (0.91, 1.70)	0.75 (0.55, 1.02)	0.91 (0.71, 1.17)	0.93 (0.71, 1.23)	1.02 (0.77, 1.34)	1.15 (0.87, 1.54)
Low income	0.95 (0.74, 1.23)	1.30 (0.96, 1.75)	0.93 (0.72, 1.21)	1.32 (0.89, 1.96)	1.05 (0.74, 1.49)	0.92 (0.68, 1.23)

Abbreviation: ADL = activities of daily living.
Data are odds ratio (95% confidence interval). We adjusted for the following potential time-constant confounders: age, age squared, sex, race, southern birthplace, education, mother's and father's educations, and height. In addition, we adjusted for the following time-varying confounders using an inverse probability weighting approach: marital status, log of household size–adjusted wealth, body mass index, self-reported comorbidities, interview wave, and our modifiers.

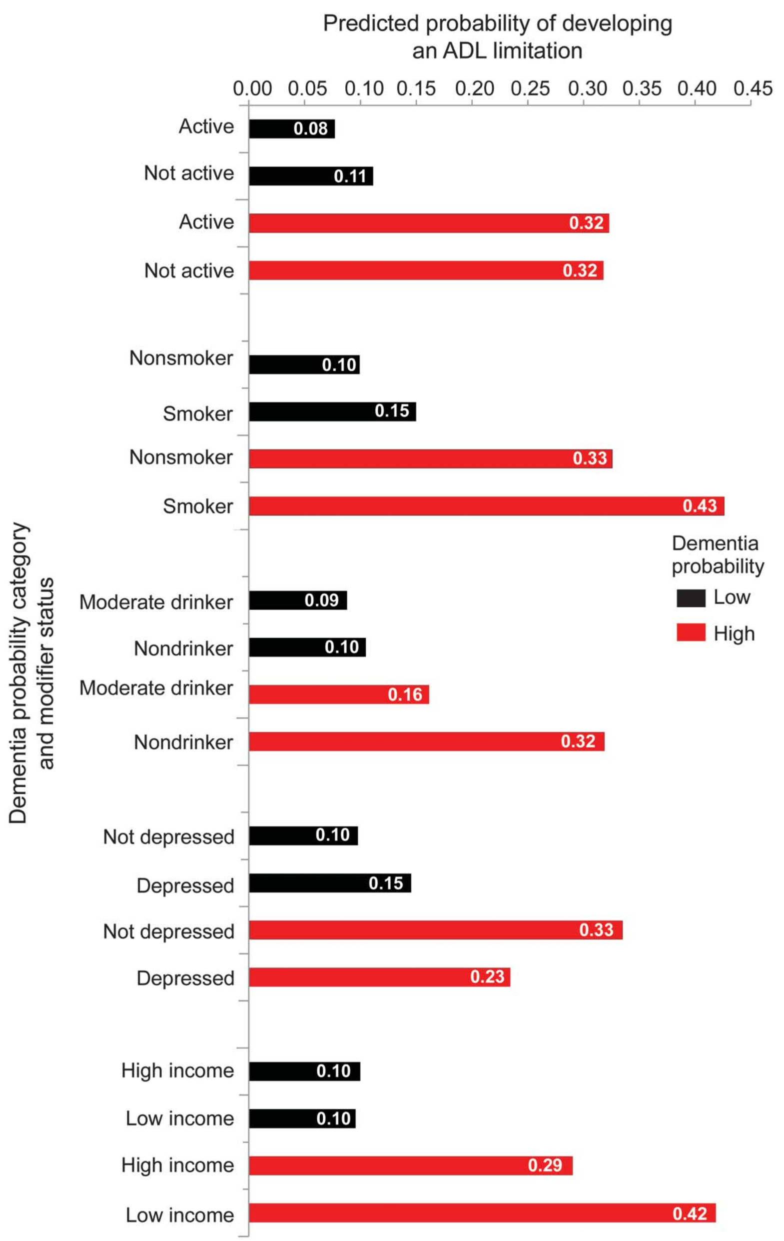
of ADL limitations and the interaction between these modifiers and dementia was also close to the null, suggesting that the relative harm of not drinking, smoking, or low income was similar regardless of dementia probability.

We also calculated the marginal probability of developing any incident ADL limitations for each combination of modifier status and lowest or highest dementia category (figure 2). For example, individuals in the lowest dementia category who are smokers have a 15.0% probability of developing any incident ADL limitation within 2 years. If a similar person is a nonsmoker, the 2-year probability of developing an ADL limitation is only 9.9%, thus not smoking predicts a 5.1 percentage point decrease in the probability of incident ADL limitations among those with low dementia probability. Smokers with the highest dementia scores have a 42.6% chance of developing an ADL limitation within 2 years, but physically active individuals with high dementia probability have only a 32.6% chance of developing any incident ADL limitation within 2 years. Not smoking predicts a 10.0 percentage point decrease in the probability of incident ADL limitations among individuals who are in the highest dementia probability category. Therefore, the absolute effect of not smoking is predicted to be larger among those with higher dementia probability. Not drinking and low income are also predicted to have larger adverse effects on the absolute probability of developing incident ADL limitations among those with high dementia probability than among those with low dementia probability.

DISCUSSION Results from this large prospective cohort study indicate that the relative impact of modifiable risk factors on incident ADL limitations was quite similar for all levels of cognitive functioning. Because disability is more prevalent among individuals with cognitive impairment, some modifiable risk factors had larger absolute benefits for individuals at high risk of dementia. This suggests that even among individuals with substantial cognitive impairment, managing conventional risk factors is very important.

Many of our individual-level modifiers are established predictors of functional decline among healthy elderly, but little evidence exists about whether these

Figure 2 **Marginal predicted probability of any ADL limitation per wave by modifier and dementia status**



Bar lengths represent actual numbers before rounding. Activities of daily living (ADL) limitations were assessed each wave (every 2 years). We adjusted regression models for the following potential confounders: age, age squared, sex, race, southern birthplace, education, mother's and father's educations, and height. In addition, we accounted for the following time-varying confounders using an inverse probability weighting approach: marital status, log of household size-adjusted wealth, body mass index, self-reported comorbidities, interview wave, and our modifiers.

advantages generalize to populations with cognitive impairment.[12] Smoking and depression have repeatedly been linked to disability measures.[13–18] Evidence on alcohol consumption and disability has been mixed.[15,19] Moderate alcohol consumption may have a protective effect for general physical functioning, but high consumption may be harmful.[20] While this study does not specifically assess the impact of initiating alcohol consumption, it suggests that efforts to reduce alcohol consumption may not improve ADL outcomes.

Research has typically focused on the impact of these modifiers on disability or functional limitations among cognitively normal adults,[13,15–17,19] although there is research on the effects of physical activity among those with cognitive impairment. A recent review found that physical activity was beneficial for physical functioning and ADL for mild, moderate, and severe dementia.[21] Some physical activity interventions have also been shown to improve physical functioning in older people with dementia.[22]

Our results on the continuing importance of modifiable risk factors among individuals with cognitive impairments have a great deal of clinical relevance. Conventional risk factors for ADL limitations, such as depression, are often undertreated among those with cognitive impairment.[5] Even traditional vascular risk factors, such as high blood pressure, dyslipidemia, diabetes mellitus, smoking, and atherosclerotic disease, may be untreated in those with cognitive impairment.[23] However, healthy risk factor profiles may help individuals with incipient dementia maintain functional independence, thereby avoiding institutionalization and decreasing caregiver burden.

We hypothesize that cognitive impairment may result in functional limitations through a multistep process. Cognitive function may be most relevant for maintaining independence among individuals with some level of physical impairments, who need to adopt behavioral accommodations or adaptive equipment to maintain independence. Because conventional risk factors delay physical impairments, they are very valuable for delaying dependence among individuals with cognitive impairment. For example, physical activity, smoking, alcohol use, and depression have all been linked to cardiovascular disease and other pathologies. Cognitive losses and conventional risk factors may create unfortunate cascades in which one reinforces the other, ultimately culminating in disability. For example, an individual with cognitive impairment may curtail independent leisure time walks or other physical activity because of safety concerns. Recognition of memory losses may lead to sadness and depression among older adults.

As with all observational research, we cannot rule out unmeasured confounding and therefore cannot infer that the observed effects are causal. Physical impairments may affect the risk factors we examined, thus confounding associations between, for example, physical activity and incident ADL limitations. This study only focused on incident ADL limitations and did not consider instrumental ADL, which may be more strongly correlated with cognition.[24] While the modifiable risk factors may provide ways of ameliorating the harmful effect of dementia probability, dementia probability is still a strong risk factor for incident ADL limitations. We do not have information on lifetime behavior history and cannot determine whether the beneficial associations are only present among those who have always practiced healthy behaviors. In addition, our measure of depression may not capture differences in depression severity appropriately in individuals with cognitive impairment. Differences in depression severity may be one possible explanation for the unexpected finding that depression may be less harmful, in relative terms, among those with cognitive impairment. We do not know when exactly within the 2-year time period between assessments that the ADL limitation developed. However, we used information on cognitive status and health modifiers from the wave before ADL assessment to avoid reverse causation. Finally, we did not examine disability fluctuations in this study. An exploratory analysis of our data found that those in the highest dementia probability category had lower odds of transitioning out of ADL limitations than those in the lowest dementia probability category. Therefore, by not examining fluctuations in ADL disability, we believe that our results are conservative estimates of the beneficial effects of our health modifiers. Because those with the highest dementia probability are the least likely to transition out of the disability state, preventing the onset of ADL limitations is important.

Among the strengths of this study is that it included a nationally representative sample with a long prospective follow-up; the longitudinal data allowed construction of a statistical model reflecting the hypothesized temporal sequencing of these factors. Given the potential dynamic feedback between cognitive impairment and other risk factors, we used IPW, currently the best available statistical tool to handle time-varying confounders and selective attrition. By using imputed dementia categories, we were able to use information from proxy reports of cognitive status instead of excluding individuals with more severe cognitive impairments. We examined both relative and absolute effects; absolute effect estimates are most relevant for evaluating public health impact.[25]

Smoking, not drinking, and having low income may increase the risk of incident ADL limitations among those with cognitive impairments. This finding has critical importance for clinicians, patients, and family members of individuals with cognitive impairments or incipient dementia. By managing conventional risk factors, it may be possible to stave off dependencies, maximize quality of life, and minimize caregiver burden.

AUTHOR CONTRIBUTIONS

Pamela M. Rist: drafting/revising the manuscript for content, including medical writing for content, study concept or design, and analysis or interpretation of data. Benjamin D. Capistrant, Qiong Wu, and Jessica R. Marden: interpretation of data and revising the manuscript for content. M. Maria Glymour: obtaining funding, study concept or design; interpretation of data, revising the manuscript for content, and supervision.

STUDY FUNDING

This work is/was supported by the Telemedicine and Advanced Technology Research Center at the US Army Medical Research and Materiel Command through award W81XWH-12-1-0143. Dr. Capistrant was supported by the NIH (T32 HD007168 and R24 HD050924).

DISCLOSURE

P. Rist has received funding from a training grant from the National Institute of Aging, from the Rose Traveling Fellowship Program in Chronic Disease Epidemiology and Biostatistics from the Harvard School of Public Health, and from a travel fund from the Department of Epidemiology at the Harvard School of Public Health. B. Capistrant receives funding from 2 NIH grants (T32 HD007168 and R24 HD050924). Q. Wu and J. Marden report no disclosures relevant to the manuscript. M. Glymour has received funding from the NIH, the Robert Wood Johnson Health & Society Program, the American Heart Association, and the Telemedicine and Advanced Technology Research Center at the US Army Medical Research and Materiel Command through award W81XWH-12-1-0143. Go to Neurology.org for full disclosures.

Received June 29, 2013. Accepted in final form January 28, 2014.

REFERENCES

1. Royall DR, Lauterbach EC, Kaufer D, et al. The cognitive correlates of functional status: a review from the Committee on Research of the American Neuropsychiatric Association. J Neuropsychiatry Clin Neurosci 2007;19:249–265.
2. Gaugler JE, Kane RL, Kane RA, Clay T, Newcomer R. Caregiving and institutionalization of cognitively impaired older people: utilizing dynamic predictors of change. Gerontologist 2003;43:219–229.
3. Jette AM. Toward a common language for function, disability, and health. Phys Ther 2006;86:726–734.
4. Verbrugge LM, Jette AM. The disablement process. Soc Sci Med 1994;38:1–14.
5. Dorenlot P, Harboun M, Bige V, Henrard JC, Ankri J. Major depression as a risk factor for early institutionalization of dementia patients living in the community. Int J Geriatr Psychiatry 2005;20:471–478.
6. Juster FT, Suzman R. The Health and Retirement Study: an overview. J Hum Resour 1995;30(suppl):7–56.
7. Heeringa SC. Technical Description of the Asset and Health Dynamics (AHEAD) Sample Design. Report of the Survey Design and Analysis Unit. Ann Arbor, MI: Institute for Social Research, University of Michigan; 1995.
8. St. Clair P, Blake D, Bugliari D, et al. RAND HRS Data Documentation. Santa Monica, CA: RAND Center for the Study of Aging; 2010.
9. Wu Q, Tchetgen Tchetgen EJ, Osypuk TL, White K, Mujahid M, Glymour MM. Combining direct and proxy assessments to reduce attrition bias in a longitudinal study. Alzheimer Dis Assoc Disord 2013;27(suppl):207–212.
10. Steffick DE, Wallace RB, Herzog R, Ofstedal MB, Fonda S, Langa K. Documentation of Affective Functioning Measures in the Health and Retirement Study. HRS/AHEAD Documentation Report. Ann Arbor, MI: Survey Research Center, University of Michigan; 2000.
11. Hernan MA, Brumback B, Robins JM. Marginal structural models to estimate the causal effect of zidovudine

on the survival of HIV-positive men. Epidemiology 2000;11:561–570.
12. Stuck AE, Walthert JM, Nikolaus T, Bula CJ, Hohmann C, Beck JC. Risk factors for functional status decline in community-living elderly people: a systematic literature review. Soc Sci Med 1999;48:445–469.
13. Eriksen W, Natvig B, Rutle O, Bruusgaard D. Smoking as a predictor of long-term work disability in physically active and inactive people. Occup Med 1998;48:315–320.
14. Haas AL, Eng C, Dowling G, Schmitt E, Hall SM. The relationship between smoking history and current functioning in disabled community-living older adults. Ann Behav Med 2005;29:166–173.
15. Klijs B, Mackenbach JP, Kunst AE. Obesity, smoking, alcohol consumption and years lived with disability: a Sullivan life table approach. BMC Public Health 2011;11:378.
16. Schmitz N, Kruse J, Kugler J. Smoking and its association with disability in chronic conditions: results from the Canadian Community and Health Survey 2.1. Nicotine Tob Res 2007;9:959–964.
17. Takashima N, Miura K, Hozawa A, et al. Cigarette smoking in middle age and a long-term risk of impaired activities of daily living: NIPPON DATA80. Nicotine Tob Res 2010;12:944–949.
18. Schillerstrom JE, Royall DR, Palmer RF. Depression, disability and intermediate pathways: a review of longitudinal studies in elders. J Geriatr Psychiatry Neurol 2008;21:183–197.
19. Karlamangla AS, Sarkisian CA, Kado DM, et al. Light to moderate alcohol consumption and disability: variable benefits by health status. Am J Epidemiol 2009;169:96–104.
20. Oslin DW. Alcohol use in late life: disability and comorbidity. J Geriatr Psychiatry Neurol 2000;13:134–140.
21. Blankevoort CG, van Heuvelen MJ, Boersma F, Luning H, de Jong J, Scherder EJ. Review of effects of physical activity on strength, balance, mobility and ADL performance in elderly subjects with dementia. Dement Geriatr Cogn Disord 2010;30:392–402.
22. Potter R, Ellard D, Rees K, Thorogood M. A systematic review of the effects of physical activity on physical functioning, quality of life and depression in older people with dementia. Int J Geriatr Psychiatry 2011;26:1000–1011.
23. Deschaintre Y, Richard F, Leys D, Pasquier F. Treatment of vascular risk factors is associated with slower decline in Alzheimer disease. Neurology 2009;73:674–680.
24. Park DC. Psychological issues related to competence: cognitive aging and instrumental activities of daily living. In: Willis SL, Schaie KW, Hayward M, editors. Societal Mechanisms for Maintaining Competence in Old Age. New York: Springer; 1997:66–80.
25. Szklo MF, Nieto J. Epidemiology: Beyond the Basics. Sudbury, MA: Jones and Bartlett; 2000:408–430.